

PSYCHOLOGY TEACHERS UPDATE

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AN INTRODUCTION TO
PSYCHONEUROIMMUNOLOGY

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PSYCHOLOGY TEACHERS UPDATE

Psychology Teachers Update is designed to give a brief overview of the main developments in the different areas of psychology. There is a proliferation of journals and research, and it is very difficult to keep abreast of the latest trends, particularly in the many and varied areas of psychology.

Each issue of Psychology Teachers Update will cover a particular topic, and summarise the main research directions and findings in the last ten to fifteen years approximately. The aim is to give teachers the feel of what is happening in that area of psychology.

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Introduction

Psychoneuroimmunology (PNI) ⁽¹⁾ can be defined as "the inter-relationship between psychological, neuroendocrinological and immunological factors" (Johnston 1994). Straub (2002) preferred the "interaction of psychological, neural and immunological processes in stress and illness" ⁽²⁾.

The key development for PNI was the discovery, since the mid-1980s, of physiological links between the nervous system and the immune system.

Historically, it has always been believed that emotional states can affect physical illness from Galen, two thousand years ago, who felt that melancholic women were prone to cancer of the reproductive organs due to an excess of "black bile". However, until recently, science and medicine had doubted the role of emotions in causing illness.

Perhaps for the first time, the science of psychoneuroimmunology helps to provide a rational basis for psychosomatic medicine which for decades has tended to be marginalised as a subject of limited scientific merit (Song and Leonard 2000 pviii).

Arthur Schopenhauer noted that all truth passed through three stages - ridicule, violently opposed, and then accepted as self-evident. PNI is between stages one and two (Song and Leonard 2000).

STRESS AND THE IMMUNE SYSTEM

Robert Ader is sometimes quoted as the founder of PNI because of his chance findings of the psychological effects on the immune system. He was classically conditioning rats with saccharin-flavoured water and a nausea-inducing immune-suppressing drug (cyclophosphamide).

Based upon the principles of Pavlov (1927) (figure 1), the rats learnt to be sick with just the saccharin-flavoured water. So strong was the classically conditioned response that the water suppressed the immune system, made the animals vulnerable to disease, and they died (Ader and Cohen 1975; 1985).

There seems to be two routes of communication between the brain and the immune system:

- a) Physical communication with lymphocyte cells.

- | | | | |
|----|------------------------------------|---|---------------------------------|
| 1. | Unconditioned
Stimulus (UCS) | → | Unconditioned
Response (UCR) |
| | cyclophosphamide | | nausea/immune suppression |
| 2. | Neutral stimulus | → | UCR |
| | saccharin-flavoured water
+ UCS | | |
| 3. | Conditioned stimulus (CS) | → | Conditioned response |
| | water | | immune suppression |

Figure 1 - Conditioning of the immune response in rats by Robert Ader.

The hypothalamus is the part of the brain which monitors the activity of the immune system. T cells activated by antigens release lymphokines, which are chemically similar to neurotransmitters, and they trigger brain cells (Straub 2002).

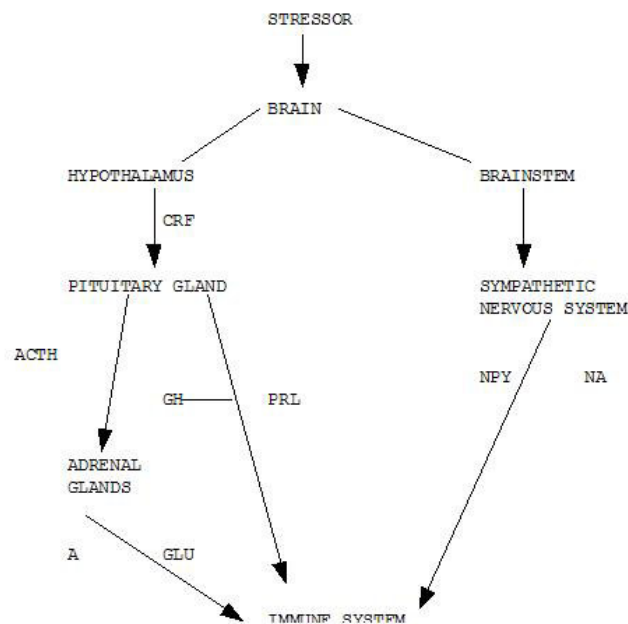
b) Biochemicals

For example, ACTH lowers white blood cell divisions (Blalock 1997). The interaction between stress and the immune system shows a complex web of communication within the body.

Put simply, the stressor activates the hypothalamus to release corticotrophin-releasing factor (CRF) which triggers the pituitary gland and also the adrenal glands. The hormones produced, including glucocorticoids, affect the immune system.

Meanwhile, the stressor stimulates the brainstem and activates the sympathetic nervous system. The consequent biochemical changes affect immune organs. Figure 2 shows the biochemicals released during stress that affect the immune system. Most of which inhibit immune activity.

Stress seems to reduce the ability of B and T cells to divide, make NK cells attacking tumours less efficient, and T cells produce less immune chemicals like interleukin-2 and gamma-interferon. Specifically adrenaline inhibits the ability of certain lymphocytes to release chemicals to kill invaders, and corticosteroids prevent lymphocytes maturing. Overall the effect is to reduce immunocompetence (3).



CRF = corticotrophin-releasing factor; ACTH = adrenocorticotrophic hormone; GLU = glucocorticoids; GH = growth hormone; PRL = prolactin; NA = noradrenaline; NPY = neuropeptide Y; A = adrenaline

(After Song and Leonard 2000)

Figure 2 - Basic biochemical relationship between stress and the immune system.

Chronic and Acute Stress

The effect of stress upon the immune system varies depending upon the length of the stressful event. In the case of short-term (or acute) stress, the immune system increases activity for a few minutes (between 5-15 minutes).

In evolutionary terms, a short-term stressor may involve running away briefly, and this means breathing more air, and the possibility of more microbes entering the body. Thus the need to increase immune efficiency. But long-term (or chronic) stress depresses the immune system (Evans et al 1997).

Table 1 shows immune functions known to react differently to chronic and acute stress.

IMMUNE FUNCTION	CHRONIC STRESS	ACUTE STRESS
Number of CD8+ cells	down	up
Number of NK cells	down	up
sIgA secretion	down	up

(After Evans et al 2000)

Table 1 - Immune responses that are different between chronic and acute stress.

Chronic and acute stress also interact. Male volunteers who had experienced recent chronic life stress had a poorer immune system response to a twelve-minute acute stress task (mental arithmetic) (Song and Leonard 2000).

A study of US soldiers on army training, by the United States Army Research Institute of Environmental Medicine (USARIEM), found increased cortisol and reduced immunity over four to six weeks of the course, but after three days rest, the levels were back to normal (Sternberg 2000).

PNI tends to focus upon two main areas:

i) The role of stress in making individuals vulnerable to acquiring illness; ie: stress suppresses the immune system (immunosuppression).

ii) The role of stress upon the outcome of the illness; ie: stress leads to a poorer outcome.

Stress Suppresses the Immune System

The early research in this area included the effects on the immune system of divorce, taking medical school exams, and caring for a partner with Alzheimer's disease (Kennedy et al 1988).

Overall there is evidence of less lymphocytes in individuals after the death of a spouse, divorce, or unemployment, in children with families under stress, and in astronauts returning from space travel (White 1998). Table 2 lists stressors found to suppress the immune system.

Stressful life events - eg: examinations, unemployment
Loneliness and poor social support
Relationship stress/Marital conflict
Separated women/Husband bereaved/Depression in bereavement
Caring for ill partner
Negative mood/Anxiety
Natural disasters

More flu and colds, herpes virus infections (cold sores and genital lesions), chicken pox, mononucleosis (glandular fever), Epstein-Barr virus (glandular fever)

Stress produces: less NK cells
 less T cells
 reduced total lymphocytes

Table 2 - Stressors and the immune system.

The two classic studies come from Kiecolt-Glaser, Glaser et al (1986), and Kiecolt-Glaser, Fisher et al (1987).

The first study took blood samples from medical students one week before their examinations and two days after. The latter sample showed less NK cells, altered T cells, and less cytokine production. There was evidence of a "dose-response" relationship: students with the highest levels of stress or tendency to overreact to stressful events showed the lowest response in the immune system in the examination week (Kiecolt-Glaser, Garner et al 1984).

In the other study (Kiecolt-Glaser, Fisher et al 1987), blood samples were taken from 38 married women and 38 separated ones. The latter group showed a lower percentage of NK cells and T-helper lymphocytes.

Cohen et al (1991) working at the Common Cold Research Lab with 394 healthy volunteers who received nasal drops of a cold virus (respiratory virus influenza A) or saline before being questioned.

For each participant, a stress index score was acquired based on life events, perceived stress, and negative affect (mood). The results were a positive correlation between the rate of clinical cold and the stress index score. Furthermore, those with higher stress scores showed less antibodies in nasal-wash samples.

Technically, a cytokine called interleukin-6 (IL-6) was higher in those with severe cold symptoms, and with higher stress scores. It could be that increased production of IL-6 is a sign that stress is affecting the body (DANA 2000). This study was able to show that stress influences the immune system in a clear way.

However, the effect of different stressors upon the immune system is not always the same. Arnetz et al (1987) compared three groups of Swedish women: unemployed with support from self-help groups, unemployed with no support, and employed. There was no difference between the groups in the numbers of B and T cells in the blood, but the unemployed women's immune systems were less reactive to antigens, especially for those unsupported unemployed women.

Similar negative effects of unemployment and lack of social support have been found among 235 East German migrants to West Berlin (before the fall of the Berlin Wall) (Schwarzer et al 1994).

The timing of the stressor may also be relevant. Evans et al (1988) felt that four days before the onset of an illness was key.

Using the detailed nine-week diaries of thirty UK undergraduates, the researchers found evidence of a greater number of "less desirable events" four days before the illness than four days before those who did not develop illness.

Other research has questioned this "four day dip" in the immune system. Stone et al (1994) found a time lag of one-two days between desirable events and increased secretory-immunoglobulin (sIgA) (found in mucus).

Based on the analysis of a three-month diary of fifteen adults with sickle cell disease, Porter et al (2000) found a link between stress two days previous and increased pain.

Evans and Edgerton (1991) looked at mood generally and symptoms of illness based upon the diaries of sixty-five administrative staff over a ten-week period. Through factor analysis, the moods reported were reduced to three main types - happiness, tense depression, and hostile depression.

Cold symptoms were significantly correlated with tense depression, and neck and headaches with hostile depression. Other research has shown that patients with

major depression showed a reduced number of lymphocytes (Song and Leonard 2000).

Depression can be linked to physical illness (eg: heart disease). Musselman et al (2000) focused upon sticky platelets in the blood, which clot to prevent bleeding. Having too many can lead to heart disease. This research found that a small group of depressed individuals had 41% more sticky platelets than non-depressed individuals. Other research has found that SSRI (selective serotonin reuptake inhibitors) anti-depressants reduced the number of sticky platelets in the blood (DANA 2000).

However, there is no consensus of opinion on the impact of depression upon immune functions with inconsistent findings (Evans et al 2000). Depression does appear, for example, to accelerate the progression of HIV/AIDS (Vassend et al 1997), but this may be due as much to the stress reaction of diagnosis and the illness as to depression suppressing the immune system.

Physical illness or injury are examples of internal stressors, and these, like drugs of abuse, can change the immune system. Table 3 gives some examples of internal stressors and their effect on the immune system (Song and Leonard 2000).

STRESSOR	EFFECT ON IMMUNE SYSTEM
<u>Physical changes</u>	
Stroke	Reduced NK cell function 2 wks-7 mths after
Ageing	Reduced activity of phagocytic cells (neutrophils and monocytes); reduced NK cell activity
Chronic Fatigue Syndrome	Reduction in total IgG (immunoglobulins)
<u>Drugs of abuse</u>	
Benzodiazepine (tranquillizers) (eg: alprazolam)	Immunoenhancing effects
Chlorpromazine (neuroleptic)	Inhibits TNF
Alcohol	Reduced T cell numbers; elevated antibodies in blood
Cocaine	Inhibition of T cell function; activation of adrenal gland and consequent increase release of glucocorticoids on immune system
Cannabis	Reduced IgG; reduction in T cell production (blastogenesis)
Morphine/heroin	Reduced T cell numbers; suppression of NK cell activity

Table 3 - Effects on the immune system of internal stressors (4) and drugs of abuse.

Stress Leads to Poorer Illness Outcomes

Two types of experimental study have been used to test the effect of stress upon the outcome of illness - immune response to vaccination, and wound healing time.

1. Immune Response to Vaccination

It is seen as unethical to vaccinate individuals solely for psychoneuroimmunology research purposes, but ongoing vaccination programmes can be used. The most obvious measure of immune functions to use is the number of virus-specific antibodies produced.

Kiecolt-Glaser et al (1996) compared elder carers of spouses with progressive dementia with matched controls during the routine seasonal influenza virus vaccine. The carers had clear evidence of compromised immunity.

Caregivers in other similar studies had been found to have higher cortisol levels, which suppress antibody response to vaccination. Of 50 carers of spouses with dementia, only 16% produced a four-fold increase in antibody levels (as expected after the vaccination) compared to 40% of the 67 controls (Vedhara et al 1999).

Glaser et al (1998) found similar reduced immune responses in medical students during the examination period receiving a routine hepatitis B vaccination.

2. Wound Healing Time

The healing of wounds follows a standard process controlled by the immune system over weeks or months (table 4). Stress delays this process (involving the complement system).

1. Inflammatory stage - vasoconstriction (reduced blood to wound site) and blood coagulation.
2. Platelet activation, and release of growth factors which stimulate migration of phagocytes to wound site.
3. Replication of cells for tissue regeneration and capillary regrowth.

Table 4 - Stages in wound healing.

Using standardised punch biopsy wounds, stressed mice took 27% longer to heal than unstressed mice (Kiecolt-Glaser, Page et al 1998), for example. A correlation of 0.82 for healing time and stress levels.

While the same dental students given a wound three days before an examination took 40% longer to heal compared to the control wound (received during the summer holidays) (Marucha, Kiecolt-Glaser and Favagehi 1998). Every student took longer to heal the wound given before the exam.

Caregivers of Alzheimers sufferers took 25% longer to heal than controls. It took an average of 48.7 days for a 3.5mm punch wound to heal among thirteen carers as opposed to 39.3 days in the control group (Kiecolt-Glaser, Marucha et al 1995).

On the other hand, positive mood can have benefits for immune functions (eg: Johnston et al 1999: progression of motor neurone disease), particularly humour (Newman and Stone 1996).

Emotional expression can influence illness outcome. The repression or inexpression of negative emotions (sometimes called "type C" behaviour) links to illness, while emotional expression (through writing or discussion) can be beneficial (see work of Pennebaker, for example, 1997).

There are two theories about the effect of stress upon wound healing (and the immune system) (Straub 2002):

i) Indirect effect hypothesis

Stress encourages "maladaptive behaviours" (eg: sleep loss, poor diet) which disrupt the immune system (eg: Conway et al 1981). Thus stress indirectly suppresses the immune system.



For example, deep sleep is associated with the secretion of growth hormone (GH) which activates macrophages to kill bacteria at a wound site. Loss of sleep, through stress and as a stressor itself, would reduce GH secretion and delay healing (Leprout et al 1997).

ii) Direct effect hypothesis

The physiological reaction to stress suppresses the immune system. The activation of the sympathoadrenomedullary (SAM) system and the hypothalamic-pituitary-

adrenocortical (HPAC) system produce immunosuppression because T cells and B cells have receptors for corticosteroid hormones, and lymphocytes for catecholamine (adrenaline and noradrenaline) (Straub 2002).

STRESS → PHYSIOLOGICAL → SUPPRESSED
 REACTION IMMUNE SYSTEM

Chemically reducing the release of corticosteroids in stressed mice leads to wound healing as long as the control group (Kiecolt-Glaser, Page et al 1998).

Animal Models and Studies

The use of animal models and studies have produced three main conclusions about the immune system (Song and Leonard 2000):

i) Alterations in the immune response can be conditioned;

ii) Immune functions can be altered by electrical stimulation or surgical lesions of particular brain areas; eg: olfactory bulbectomy ⁽⁵⁾ in rats and reduced spleen weight (Song and Leonard 1995), or stimulation of the amygdala;

iii) Stress can affect the growth of tumours.

Experimental work with animals has been able to deliberately increase stress levels and see the effect upon the immune system. Environmental stressors include noise, bright light, odour, and housing conditions, which all reduce antibody production. While neurogenic stressors increase the number of total leucocytes and neutrophils, and suppress NK cell cytotoxicity.

Neurogenic stressors include forced swimming in cold water or mild electrical footshocks. Psychological stressors, like predator exposure, also reduced NK cell cytotoxicity among other things (Song and Leonard 2000).

USE OF RATS IN PSYCHONEUROIMMUNOLOGY

Laudenslayer et al (1988) compared the number of T cells in the blood of rats receiving regular mild (but unpleasant) electric shocks. Rats who could control the electric shocks had the same number of T cells as the unstressed rats (receiving no electric shocks), while those animals receiving uncontrollable shocks had the least number of T cells. This links to work (eg: Langer and Rodin 1976) that has shown how perceived control can reduce the effects of stressors ⁽⁶⁾.

Visintainer et al (1983) used the same experimental design but implanted tumours in the rats to see if the immune system fought their growth. Of those rats receiving the uncontrollable electric shocks, for only 27% did the tumour not develop further compared to the majority (73%) of those receiving controllable shocks.

Ben-Eliyahu et al (1991) injected the malignant tumour cells into rats who were then stressed with electric shocks and loud noise one hour or 24 hours after the injection. The former group showed the larger growth

of malignant cells because of the reduction in NK cell cytotoxicity against the tumour.

But Mestel (1994) quotes similar work with rats that found that tumours transplanted before the stress became larger with the stressful events, and tumours transplanted after the stressful events were reduced. This suggests that the immune system rebounds after stress.

Table 5 summarises some of the main findings from studies with rats.

TYPE OF STRESSOR	IMMUNE CHANGES
Restraint - animals in restricted cages	Reduced NK cell activity; reduced lymphocyte proliferation
Mild electric shocks to tail or feet	Reduced NK cell activity; reduced lymphocyte proliferation
Crowding	Reduced antigen response
Paired male rats	Defeated animal in fights has lowered antibody response
Maternal deprivation	Reduced lymphocyte function

(After Song and Leonard 2000)

Table 5 - Different stressors and immune changes in rats.

Stress and Cancer

Cancer is not one disease, but more than 250 types where cells multiply abnormally and out of control, forming a tissue mass called a tumour. Malignant cells can also migrate to other parts of the body and cause damage there in a process called metastasis (Straub 2002). Table 6 lists the main types of cancer.

Carcinomas	attack cells on surface of body; eg: skin
Sarcomas	muscles, bones and cartilage malignant cells
Lymphomas	cancers formed in lymphatic system
Leukaemias	cancer of blood and blood-forming system; eg: bone marrow

Table 6 - Types of cancer.

The everyday assumption that stressful events are related to cancer has a long history (7). For example, Snow (1893) noted that women with breast or uterine cancer had a "general liability to the buffets of ill-fortune".

Sontag (1979), in the book "Illness as Metaphor", argued that cancer was the "outward expression" of the increasing stress of 20th (and 21st) century life. The belief among patients that "their disease results from too much stress" is common (McGee 1999).

This idea can be seen as an extension of the view of psychoanalyst George Groddeck that cancer was a form of symbolic pregnancy (Petticrew 1999).

In surveys of the general public, the belief that stress is a risk factor for cancer is held by many people. This belief can be classed as "lay epistemology". But it is not just the general public:

Textbooks also disagree: medical texts tend to dismiss the theory outright while reviews and textbooks in health psychology are less dismissive and tend to suspend judgement (Petticrew 1999 p53).

But what does the research say about the relationship between stress and cancer (8)?

Chen et al (1995), in a typical study, found that women with breast cancer were twelve times more likely to have experienced severe life events in the five years before diagnosis. In this type of study, the women were

interviewed about their recent life events after a biopsy, but before they knew the results; ie: whether the growth was cancerous (malignant) or not (benign).

The studies are not unanimous because other research has found opposite results. For example, among 332 women from Leeds, those diagnosed with breast cancer had generally experienced less stressful events in the previous five years before diagnosis (Protheroe et al 1999).

There are a number of problems with the research design used in these studies:

i) They are retrospective studies asking participants to recall life events over a certain period of time. This depends upon the accuracy of recall of past experiences which is far from perfect;

ii) In some cases, the participants knew their diagnosis before being interviewed. This could lead to a selectivity of recall for negative or stressful life events if the participants knew that they had breast cancer (McGee 1999) (known as recall bias);

iii) The matching of the controls. It is necessary to have a comparison group who are not diagnosed with cancer, but they should be of similar age and social characteristics as the cases. For example, in the Protheroe et al study, the controls were younger (by an average of 10.6 years);

iv) Limited control of confounding variables;

v) The same stressful life event may affect people in different ways, and so an additive score of stressful events is of limited use. The idea of common stress scores for life events was used by Holmes and Rahe (1967) in the Social Readjustment Rating Scale (SRRS). But the impact of a life event will be mediated by variables like predictability and perceived controllability.

The best type of research design is the random controlled trial, but this is impossible here - "you cannot randomise some people to experience many stressful life events and others to remain stress-free" (Petticrew 1999) - and, if possible, unethical.

A feasible design for this type of research is the prospective study. This starts with the life event(s) and follows the participants to see who develops cancer. For example, those suffering bereavement (Jones et al 1984) or prisoners of war from World War II and the Korean war (Keehn 1980). Both these studies did not find increasing

mortality from cancer compared to controls.

Why are the studies contradictory in their findings? Petticrew (1999) had a simple answer - methodological weaknesses. In a review of 29 studies of the relationship between stressful life events and breast cancer, the "worse the quality of the study, the more likely it was to show a positive association", while "Pooled the higher-quality studies revealed no significant association" (Petticrew 1999 p53).

Stress may not cause cancer, but what happens after the diagnosis can be important for the outcome of the illness. In other words, the cancer survival times or cancer recurrence.

Ramirez et al (1989), in a British study, looked at the relationship between severe life events and recurrence of breast cancer in fifty post-operation disease-free women. Compared to the control group, stressful life events increased the relative risk of relapse (table 7).

Any stressful event	2.50
Non-severe life events	2.00
Severe stress	5.67
Any severe stressor	9.00

Table 7 - Relative risk of relapse of breast cancer based on stressful life events.

However, these results have been challenged (for example for being a cross-sectional study; Ogden 2004). The type of breast cancer is an important variable in the relationship between stress and relapse (Barracclough 1994). But Barracclough's work used older women, and a shorter follow-up period (Ogden 2004).

Greer et al (1979) found that among 69 women diagnosed with breast cancer, those who denied it or fought it were more likely to be free of the illness five years later compared to those who accepted it.

In the fifteen-year follow-up, the "fighting spirit" was associated with survival more than denial, helplessness, or acceptance (Greer 1991). While Gidron et al (2001) have shown in 49 Israeli women that helplessness, not pessimism, was linked to poor outcomes after four months of breast cancer.

Andrykowski et al (1994) noted the role of "anxious preoccupation" associated with poorer post bone marrow transplant survival.

Steptoe and Ayers (2004) warned of a lack of consistent evidence about the impact of coping responses.

A full review appears in Petticrew et al (2002).

Other factors of coping that appear beneficial are an active, engaged coping style, and optimistic disposition at the time of diagnosis (Straub 2002). Emotional support is also important.

Applying this idea with group therapy, Spiegel et al (1989) offered twenty-four women diagnosed with metastatic breast cancer the opportunity to talk about the experience and emotions of the illness. The focus of the group was supportive (ie: to reduce stress and negative emotions about the illness). There was a control group of 24 women given the usual care. The women in the group therapy were less distressed by the illness, reported less pain and lived longer (mean survival time after diagnosis of 36 months to 19 for the control group). However, it may not have been the group therapy itself that was beneficial, but that the women here supported each other to maintain the medication/treatment (Johnston 1994).

Individuals who feel "socially connected" (ie: network of caring friends) are less likely to die of all types of cancer compared to socially isolated individuals (Reynolds and Kaplan 1990).

Specific techniques like stress management skills can benefit patients after surgery in terms of reducing recurrence (eg: Fawzy et al 1993: six year survival with malignant melanoma - skin cancer). Whatever other benefits, such programmes give patients quality of life benefits (Kilbourn and Durning 2003).

HIV/AIDS and Stress

Acquired immunodeficiency syndrome (AIDS) is caused by human immunodeficiency virus (HIV), and the immune system is attacked leaving the individual vulnerable to opportunistic infection (eg: pneumocystis carinii pneumonia - PCP) (Staub 2002). HIV is a retrovirus which injects copies of its own DNA into T cells, thus killing them.

The number of T cells are also reduced because HIV infection increases noradrenaline levels in the body, and this, as part of the stress reaction of the body, reduces the number of T cells (Straub 2002). Healthy T cell quantities are approximately 1000 per cubic milliliter, and this is reduced to 100 during AIDS (Straub 2002).

The course of HIV can be divided into four stages (Straub 2000) (table 8).

STAGE	SYMPTOMS	APPROX TIME
1. Immune system destroys most of virus	mild eg: sore throat, fever	1-8 wks
2. Latency period: HIV replicating, but T cells concentration reducing	no obvious, except swollen lymph nodes	mths or yrs
3. Immune function impaired and opportunistic infections occur	Opportunistic infection	mths or yrs
4. All immunity lost & full-blown AIDS occurs	eventually death	mths or yrs

Table 8 - Stages of HIV.

There are a number of studies that have looked at the role of stress in the progress and outcome of HIV infection through the four stages of its development. In other words, does stress produce a swifter progression of the HIV infection?

Kemeny et al (1995) attempted to answer this question with a study of gay men who had recently suffered the death of a partner. Those men who were HIV-infected showed a reduction in mitogen related measures during bereavement, and this was independent of medication and recreational drug use.

In a nine-year longitudinal study, Cole et al (1996) followed the progress of 72 initially healthy HIV-

infected gay men. The stress of concealment of gay identity (by "rejection-sensitive individuals") was found to be the strongest predictor of disease progress. While, using the same research group, Reed et al (1994) found that resigned acceptance of HIV status (eg: "I tried to accept what might happen") predicted the lowest survival times.

Evans et al (1997) found that the effect of stress was greatest on the progression of the illness if the life events occurred early in the infection.

Kalichman (1998) reviewed the general studies on PNI, and concluded that "it is reasonable to propose stress as a co-factor in the progression of HIV infection" (p177). However, he was also aware of inconsistent findings specific to HIV/AIDS.

For example, the San Francisco Men's Health Study (Burack et al 1993) of both gay and bisexual, and of HIV-positive and negative men "failed to demonstrate depression as a significant predictor of AIDS or death" (Kalichman 1998 p179), though there was a small association between depression at the beginning of the study and reduced T-helper cell count.

There are problems in measuring stress and feelings, which can account for the difference in findings. Many studies measure self-reported feelings at the start of the study, but these are not static emotions and may vary considerably: "Comparing the results of studies of different people with different statuses and at different times in their lives could be misleading" (Straub 2002).

For example, bereavement of a partner from AIDS can influence individuals differently depending on their HIV status. Mayne et al (1998) followed 100 gay men for one year after partner bereavement. HIV-positive men tended to reduce their risky sexual behaviour after bereavement due to feeling more vulnerable themselves, possibly, while HIV-negative individuals increased the behaviour through "survivor's guilt" or freedom from the burden of caring.

Cognitive factors may mediate the effects of stress: for example, self-efficacy for effective coping reduces cortisol levels in HIV-seropositive (9) men, while internal attribution of negative events reduces CD4+ cell counts in the same group (Kalichman 1998).

Cognitive-behavioural stress management (CBSM) can also be beneficial. Antoni et al (2000) offered seropositive men ten weekly 2 hour sessions of stress management and relaxation training. Not only did the treatment group report less anxiety and perceived stress compared to the control group, but six-twelve months

later they showed a significant increase in T-cytotoxic cells.

Table 9 summarises psychosocial factors which influenced the progress of HIV and AIDS.

SPEED UP PROGRESS OF ILLNESS	SLOW DOWN PROGRESS OF ILLNESS
- Negative beliefs about self	- Maintain hope
- Pessimistic outlook	- Find meaning
- Chronic depression	- Social support
- Hide gay sexual orientation	- Death of partner that frees individual from carer responsibility
- Isolation/lack of emotional support	- Self-efficacy about coping
- Recent bereavement	- Cognitive-behavioural stress management
- Resignation of fate	- Acting coping
- Internal attribution of negative events	

Deny diagnosis - evidence contradictory

Table 9 - Summary of factors that influence the progress of HIV and AIDS.

Appendix: Basics of the Immune System

"The function of the immune system is recognition and defence against foreign substances, in distinguishing what is 'self' from 'non-self' (Song and Leonard 2000 p5). It has been called a "society of interacting cells" (Krammer 2000). Immune responses involve the central nervous system and the endocrine system as well.

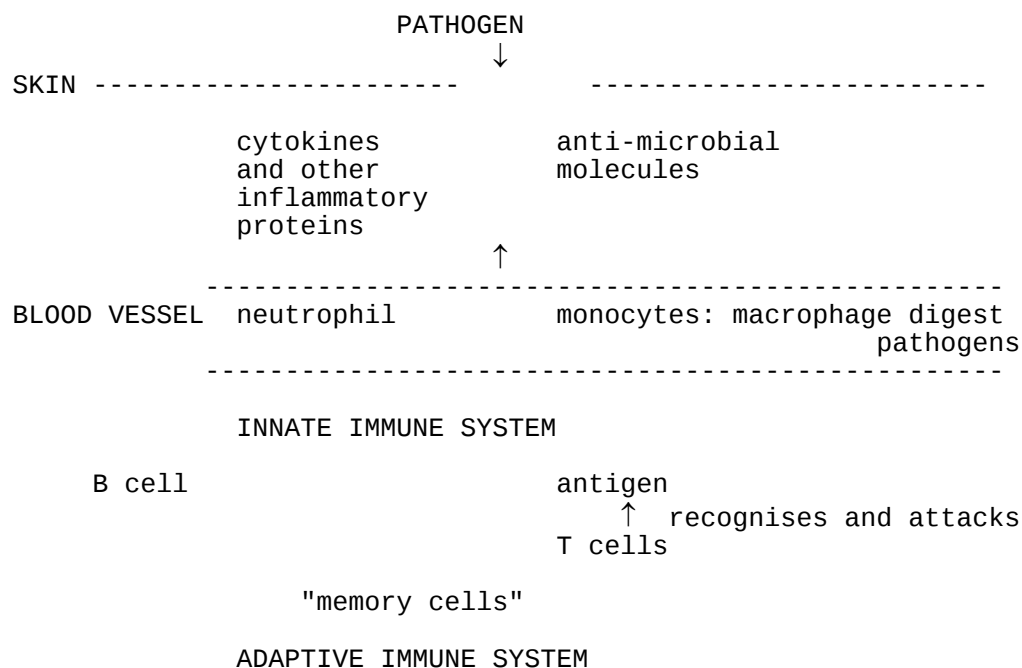
There are two kinds of immunity:

i) Innate - aspects of the immune system that are present from birth; eg: skin barrier, cough reflex, wound healing and inflammation, fever (pyrexia) (Gould and Brooker 2000);

ii) Acquired - aspects that develop after birth; eg: antibody production, immune organs like the thymus.

There will be a primary response to an antigen which is not recognised by the immune system, and after this reaction memory B cells are formed. So if the antigen reappears later, a secondary response occurs based on the memory B cells (Hubbard and Mechan 1997).

Figure 3 shows the distinction between the two kinds of immunity.



(After O'Neill 2005)

Figure 3 - Innate and adaptive immune systems.

Infections are transmitted into the human body in a number of ways, including directly through, for example, sexual intercourse, or indirectly (eg: microbes in the air).

The microbes penetrate bodily tissue and their success depends upon their number and toxigenicity (ability to produce poisons) against the body's defensive powers (ie: the immune system). Localised infections remain at the site of entry, while focal infections both remain at the point of entry and send toxins elsewhere in the body. Systematic infections affect many areas of the body (Taylor 1995). Exterior defences of the body include the skin barrier, and mucus at external access points to the body like the nostrils.

The immunity of the body has both non-specific and specific mechanisms. The former includes phagocytes which ingest microbes, or antimicrobial substances, like interferon. Specific immunity is based around antibodies (proteins) (table 10) which are produced in response to stimulation by antigens. Specific immune responses also include B and T cells.

Agglutinins	make foreign particles stick together
Precipitins	cause production of chemicals
Antitoxins	neutralise toxins
Lysins	break down foreign material
Opsomins	stimulate macrophages to engulf foreign particles

Table 10 - Types of antibodies.

There are five major kinds of immune cells:

- i) T lymphocytes;
- ii) B lymphocytes;
- iii) Monocytes;
- iv) Natural killer (NK) cells;
- v) Granulocytes.

A fine balance of cells being produced and cells dying is maintained when antigens are not present.

There are two basic immunological reactions:

- i) Humoral

B lymphocytes protect against bacteria, and B cells produce antibodies. They are best for combating bacterial or viral infections before cells are invaded;

ii) Cell-mediated

T lymphocytes from the thymus gland produce a slower-acting response. T cells secrete chemicals that attack foreign substances, particularly those inside cells.

There are three types of T cells: cytotoxic T cells (T_c) which are toxic to foreign substances; helper T cells (T_H) which enhance T_c with chemicals like interleukin-2; and suppressor T cells (T_s) suppress the immune functions.

The key organs in the body related to the immune system are the spleen, which produces B and T cells, and removes worn-out red blood cells; the tonsils which filter out micro-organisms in the respiratory tract; and the thymus helps T cells mature, and produces the hormone thymosin which stimulates T cells.

Other key organs include bone marrow, which is the origin of all immune cells, and lymph nodes, which act as filters for the lymph system (tissue fluid).

These immune organs are divided into primary lymphoid organs (thymus and bone marrow), and secondary lymphoid organs (eg: spleen and lymph nodes) (Lydyard and Grossi 1993b).

STAGES IN THE IMMUNE SYSTEM

1. Phagocytosis - white blood cells ingest microbes. Antigen-presenting cells (APC) carry antigen in form that stimulates lymphocytes;

2. Macrophages engulf antigens and release interleukin-1;

3. Helper T cells (T_H) release interleukin-2 which promotes cytotoxic T cells (T_c) and suppressor T cells (T_s);

4. Latter releases chemicals to promote specific B cells;

5. Macrophages and NK cells secrete interferon, which inhibits viral reproduction in uninfected cells;

6. Macrophages, NK cells and TC directly kill infected cells;

7. T_s turns off immune response as appropriate (Taylor 1995).

MEASURES USED IN STUDYING IMMUNE SYSTEM

i) Capacity of lymphocyte cells to proliferate when triggered by mitogens (stress reduces this capacity). For example, phytohemagglutinin (PHA) is an antigen-triggering substance used;

ii) Number of different types of lymphocytes in blood; eg: CD8+ cells, T cells (stress reduces the number);

iii) Level of anti-tumour activity by NK cells (reduced by stress), and tumour growth used mainly in animal research;

iv) Production of anti-bodies (immunoglobulins) produced by lymphocytes called B cells; eg: secretory immunoglobulin A (sIgA) found in saliva (decreased production by stress).

v) Wound healing time.

MALFUNCTIONING IMMUNE SYSTEM

The immune system can malfunction in three ways (Male and Roitt 1993):

i) Autoimmunity - mistakenly recognises own tissue as antigen and attacks; eg: rheumatoid arthritis;

ii) Immunodeficiency - part of immune system not able to fight infection; eg: acquired immunodeficiency syndrome (AIDS);

iii) Hypersensitivity - over-reaction of immune system relative to danger of antigen; eg: hay fever response to pollen grain.

Footnotes

1. PNI makes use of different research methods, but the lab experiment is often the most dominant with its strengths and weaknesses (Owens 2003).

2. Hans Selye (1956) gave the general definition of stress as a "non-specific response of the body to any demands made upon it".

3. Research has found that cultured pneumonia bacteria grew better with adrenaline or noradrenaline (In Brief 2000).

4. Stress has been linked to other illnesses (Bennett 2000); eg: irritable bowel syndrome (eg: Dancey et al 1998), and rheumatoid arthritis (eg: Urrows et al 1994).

5. Removal of part of the brain that receives olfactory signals (olfactory bulb).

6. Ogden (2004) summarised the theories on the relationship between control, stress and illness:

i) Control and preventive behaviour - high control allows individuals to maintain healthy behaviour;

ii) Control and behaviour following illness - high control allows individuals to change to healthy behaviour following illness;

iii) Control and physiology - control produces physiological change;

iv) Control and person responsibility - high control can lead to blaming self for failings and sense of helplessness, and produce unhealthy behaviours.

7. Psychology can be related to cancer in a number of ways (Ogden 2004):

- Initiation and promotion of cancer;
- Psychological consequences of cancer;
- Dealing with the symptoms of cancer;
- Longevity and promoting a "disease-free interval".

8. The main explanation for the relationship between stress and the development of cancer is the immune surveillance theory.

Normally NK cells, in particular, prevent spontaneous cancer cells from spreading and developing into tumours. Stress reduces the number of NK cells, and thus the cancerous cells are left to develop (Holland and Lewis 1996).

9. Seropositive is the state of testing HIV-positive, indicating infection by the AIDS virus (Straub 2002).

Glossary

Acute phase proteins	Serum proteins that increase during infection or inflammation; part of non-specific response to infection
Antibody	Protein produced in response to antigen by B cells; also known as immunoglobulins (Igs), and attack antigen
Antigen	Foreign substance (microbes, bacteria, viruses, fungi, parasites) (or "non-self") recognised by B or T cells and that stimulates the immune system
B cells/lymphocytes	White blood cells from bone marrow that produce antibodies
Basophil	White blood cell that contains hormones (eg: histamine) released in inflammation
CD4+/CD8+ cells	Subset of T helper cells
Complement system	Group of serum proteins (eg: acute phase proteins) which control inflammation
Cytokine	Chemical messenger within immune system eg: interleukins
Cytotoxicity	Ability to stop tumour growth (ie: own cell that making foreign protein)
Eosinophil	Type of white blood cell; specific role in combating parasitic worms
Gamma-interferon	Antimicrobial substance; generally proteins that increase resistance of cells to viral infection
Immunocompetence	Ability of immune system to defend the body against foreign substances
Immunoglobulins (Igs)	Any protein with antibody activity: 5 different types - G, A, M, D, E; most important = IgG; when measured in mucus called secretory-immunoglobulin (sIg) (see table 11)
Immunosuppression	Reduction in effectiveness of immune system to defend body against foreign substances

Interferon Antimicrobial protein that limits spread of viral infections to healthy cells

TYPE	FOUND IN	% TOTAL IMMUNOGLOBULIN (Turner and Owen 1993)
IgG	blood	70-75
IgA	external secretions eg: tears, saliva	15-20
IgM	serum	10
IgD	on surface of B lymphocytes	less than 1
IgE	on surface of basophils in lungs and skin	scarce

Table 11 - Types of immunoglobulin.

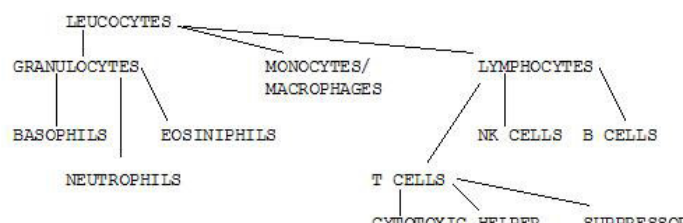
Interleukin Regulate immune cell growth and function
eg interleukin-2 (IL2); 18 different types
(Song and Leonard 2000)

Leucocytes General term for any white blood cell

CELL TYPE	% TOTAL LEUCOCYTES
Granulocytes	
Neutrophil	40-75
Eosinophil	1-6
Basophil	less than 1
Agranulocytes	
Lymphocyte	20-45
Monocyte	2-10

(After Evans et al 2000)

Table 12 - Number of different leucocytes.



(After Hayward 1998)

Figure 4 - Types of leucocytes.

Lymphocytes Immune cells programmed to recognise specific antigens and respond; main = T and B cells

Lymphokines	All non-antibody immune messengers (eg: interferons) secreted by lymphocytes
Macrophages	Immune cells that digest foreign substances (mature monocytes)
Major histocompatibility complex (MHC) proteins	Cell surface proteins coded by genes on chromosome 6; T cells only respond if MHC proteins involved
Mitogen	Chemical that stimulates B and T cell proliferation
Monocytes	Type of leucocyte; matures into macrophages
Natural Killer (NK) cells	White cells that attack tumours and previously unknown antigens (account for up to 15% of blood lymphocytes; Lydyard and Grossi 1993a)
Neutrophils	White blood cells first to wound site
Phagocytes	White blood cells that ingest foreign particles; includes monocytes, macrophages, and neutrophils; most important type are mononuclear phagocyte cells made from bone marrow stem cells
Platelets	Small cell fragments that stick together to form clots where walls of blood vessels damaged
T cells/ lymphocytes	Type of lymphocyte which recognises antigens; 3 types: cytotoxic, helper, suppressor
Tumour Necrosis Factor (TNF)	2 forms - pro-inflammatory cytokine, and T helper cytokine

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